

**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES
OF THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In Re Application of:
Minxue Zheng et al.

Confirmation No. 9085

Application Serial No. 10/667,191

Group Art Unit: 1637

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Examiner: Heather Calamita

Title: DUAL-PURPOSE PRIMERS AND PROBES FOR PROVIDING ENHANCED
HYBRIDIZATION ASSAYS BY DISRUPTION OF SECONDARY STRUCTURE FORMATION

APPEAL BRIEF

Mail Stop Appeal

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicants respectfully appeal the rejections set forth in the non-final Office Action mailed from the USPTO on December 28, 2007. As the claims under consideration have been twice rejected, this appeal is proper.

A Notice of Appeal was timely filed on March 27, 2008, along with a Request for a Pre-Appeal Brief Conference. In a Notice mailed from the USPTO on May 12, 2008, applicants were informed that the Pre-Appeal Brief Panel was unable to dispose of the issues presented to them; consequently, this case is proceeding with the appeal process.

Accompanying this paper is the fee specified in 37 C.F.R. § 41.20(b)(2) for the filing of this Appeal Brief. As this Appeal Brief is filed within two months of the May 12, 2008, mailing date of the Notice of Panel Decision, the fee under 37 C.F.R. § 1.17(a)(2) for a one month extension accompanies this paper.

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I. REAL PARTY IN INTEREST

The real party in interest is Siemens Healthcare Diagnostics, Inc., the assignee of record. The assignment documents showing the chain of title from the inventors to Siemens Healthcare Diagnostics, Inc. are recorded with the USPTO at Reel/Frame Nos. 014358/0220; 019769/0510; and 020333/0976.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals and/or interferences for this case.

III. STATUS OF THE CLAIMS

Claims 1-18 and 26-35 were rejected in the non-final Office Action and are under appeal.

IV. STATUS OF AMENDMENTS

No amendments were filed subsequent to the mailing of the non-final Office Action.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Claims 1-18 and 26-35 have two independent claims: claims 1 and 32.

As recited in claim 1, the present invention is directed to a dual-purpose primer for amplifying a target nucleotide sequence in a target molecule, wherein the target molecule has a secondary structure forming region and further wherein the target nucleotide sequence contains a site of interest proximal to or contained within the secondary structure forming region wherein the primer comprises: (a) a primer sequence complementary to a segment of the target nucleotide sequence other than the secondary structure forming region; and (b) a blocking sequence substantially complementary to a segment of the secondary structure forming region, wherein the blocking sequence disrupts formation of the unwanted secondary structure in an amplicon thereby enabling detection and amplification of the site of interest.

As recited in claim 32, the present invention is directed to a hybridization probe comprising (a) a probe nucleotide sequence complementary to a first nucleotide sequence in a target molecule, and (b) a blocking sequence substantially complementary to a second nucleotide sequence located within a secondary structure formation in the target molecule, wherein the

secondary structure formation interferes with hybridization of the probe nucleotide sequence to the first nucleotide sequence and further wherein hybridization of the blocking sequence with the second nucleotide sequence disrupts the secondary structure formation in the second nucleotide sequence such that the probe nucleotide sequence is able to hybridize to the first nucleotide sequence.

Paragraphs 0003 and 0004 of the specification discuss how intermolecular secondary structures may block hybrid formation between an oligonucleotide and its target complementary sequence (page 2, lines 5-13). Paragraph 0005 provides an example of how secondary structure formation inhibits the identification of the SNP in each of the four exons of the cytochrome P450 CYP2D6 gene (page 2, lines 14-27). Paragraphs 0006 and 0007 explain that at the time of the invention, helper oligonucleotides (described in U.S. Patent No. 5,030,557 to Hogan et al.) were used to overcome the problem of the identification of target sequences within a secondary structure forming region. The Hogan et al. helper oligonucleotide method requires the addition of a molar excess (about 5 to 100 times that of the probe) of helper oligonucleotides to the nucleic acid probe sequence to assist the probe sequence to hybridize to the target sequence; the helper oligonucleotides of Hogan et al. are about 20 to about 50 nucleotides in length (page 2, line 28, to page 3, line 4).

As explained at paragraph 0008 of the specification, the dual-purpose primers of the present invention overcome the problem in the art of detection of a target sequence within a secondary structure forming region and improve upon the method of Hogan et al. by providing a dual-purpose primer that is capable of identifying a target sequence within a secondary structure forming region with a single oligonucleotide comprised of a blocking sequence that can be substantially shorter than the Hogan et al. helper oligonucleotides and which also does not have to have perfect complementarity with the secondary structure forming region of the target molecule (page 3, lines 18-23).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. Whether the Examiner's claim interpretation is proper.
2. Whether claims 1-18 and 26-35 lack an adequate written description under 35 U.S.C. § 112, first paragraph.

3. Whether claims 1-18 and 26-35 are anticipated under 35 U.S.C. § 102(b) by Wilton et al., *Human Mutation* (1998) (hereinafter "Wilton et al.").
4. Whether claims 1, 2 and 4-7 are anticipated under 35 U.S.C. § 102(b) by USPN 5,573,906 to Bannwarth et al. (hereinafter "Bannwarth et al.").
5. Whether claims 1 and 5-8 are anticipated under 35 U.S.C. § 102(b) by U.S. Publication No. 2002/0028455 to Laibinis et al. (hereinafter "Laibinis et al.").
6. Whether claims 1, 17, and 18 are anticipated under 35 U.S.C. § 102(b) by USPN 6,268,147 to Beattie et al. (hereinafter "Beattie et al.").
7. Whether claims 27-32 are rendered obvious under 35 U.S.C. § 103(a) over Wilton et al. in view of Stratagene's 1998 Catalog (hereinafter "Stratagene").
8. Whether claim 28 is rendered obvious under 35 U.S.C. § 103(a) over Bannwarth et al. in view of Stratagene.
9. Whether claims 28-34 are rendered obvious under 35 U.S.C. § 103(a) over Beattie et al. in view of Stratagene.
10. Whether claims 10, 11, 15, and 16 are rendered obvious under 35 U.S.C. § 103(a) over Wilton et al. in view of USPN 6,054,568 to Fisher (hereinafter "Fisher").
11. Whether the Examiner's interpretation of the claim term "substantially complementary" is proper.

VII. ARGUMENT

A. THE EXAMINER'S CLAIM INTERPRETATION IS NOT PROPER

The Claim Interpretation section of the Non-Final Office Action under reply (hereinafter referred to as "NFOA, "Office Action under reply," or "Office Action") was provided in response to applicants' request in the response filed on Oct. 7, 2007 (page 10, 1st full para., last sentence) for an explanation of the Examiner's position regarding the blocking sequence (see claim 1, item (b)). The Examiner's position on the blocking sequence is that it is described with functional language warranting no patentable weight (NFOA, p.2, No. 3). Applicants' position is that the blocking sequence is properly recited as a structural feature of the claimed dual-purpose primers. Because the Examiner's claim interpretation is the basis of the dispute currently before this Honorable Board, it warrants a discussion.

In the Claim Interpretation section, the Examiner writes that the claimed primer is described functionally because no target sequences are specified for the primer and the claimed primer is anticipated by any prior art primer for which a target sequence exists or could be synthesized to carry out the functions of the primer (NFOA, p.2, No. 3). In the last full sentence at page 2 of the Office Action, the Examiner writes that "[o]nly those limitations that impart target-independent structural limitations on the claimed primer will be considered." Applicants submit that the Examiner's claim interpretation is not factually or legally correct.

Although the Claim Interpretation section of the Office Action discusses the primer generally, the individual rejections in the Office Action indicate that the issue with the claimed dual-purpose primer lies only with the blocking sequence. Directing the Board's attention to the anticipation rejections (*see, e.g.*, NFAO, p.5, 3rd full para.), there, it is stated that the only structural limitation recited in the claims is the language directed to the primer sequence of (a). Applicants appreciate the Examiner's acknowledgement that the primer sequence of (a) is in fact a structural sequence; however, applicants fail to understand how the Examiner can consider the primer sequence of (a) to be a structural limitation, but not the blocking sequence of (b). A review of the language of (a) and (b) shows that the two claim limitations recite parallel language directed to two separate structural sequences; specifically, (a) a primer sequence complementary to a segment of the target nucleotide sequence other than the secondary structure forming region and (b) a blocking sequence substantially complementary to a segment of the secondary structure forming region. Both (a) and (b) expressly recite sequences that are part of the dual-purpose primer based upon their complementarity with sections of the target molecule.

Applicants submit that the assertion that the blocking sequence is strictly a functional recitation has no factual basis. As explained in the specification, the blocking sequence prevents formation of secondary structures, which allows the dual-purpose primers to detect otherwise undetectable target nucleotides (*see, e.g.*, para. 0013, pp. 4-5; para. 0019, pp. 5-6; para. 0057, p.14; para. 0067, pp. 17-18; Example 1, para. 0096, pp. 25-26; and Figures 5 and 10). It is axiomatic that each target molecule will have a different sequence within the secondary structure forming region that will hybridize to the blocking sequence. In this respect, claiming the blocking sequence with a specific sequence of nucleotides as requested in the Office Action would make the claimed dual-purpose primer only capable of disrupting secondary structure in a single or an

extremely limited number of target molecules. Such a restriction on the claims would render any ensuing patent directed to the dual-purpose primers worthless.

Because the Claim Interpretation set forth in the Office Action is not based upon a proper factual or legal basis, applicants respectfully request that this Honorable Board not adopt the Claim Interpretation set forth in the Office Action; rather, applicants respectfully request that this Honorable Board interpret the claimed dual-purpose primers (claims 1-31) and the claimed hybridization probe (claims 32-35) to include two structural limitations: the primer or probe sequence segment of (a) and the blocking sequence segment of (b).

B. CLAIMS 1-18 AND 26-35 FULFILL THE WRITTEN DESCRIPTION REQUIREMENTS OF 35 U.S.C. § 112, FIRST PARAGRAPH

Applicants appeal the rejection of claims 1-18 and 26-35 under 35 U.S.C. § 112, first paragraph, as lacking an adequate written description. For purposes of the appeal of this issue, all claims stand together.

The gist of the written description rejection stems from the Claim Interpretation analysis discussed above. The Examiner's position on this issue is that because no specific sequence is specified for the target or the primer, the claim lacks an adequate written description.

In the written description rejection, citations are made to three Federal Circuit cases relating to 35 U.S.C. § 112, first paragraph. Each of the cited cases relates to new species of nucleic acids and/or proteins, all of which require a sequence or a method of isolation in order to establish possession of the compounds. In particular, *Fiers* relates to newly created human beta-interferon; *Amgen* relates to newly created human erythropoietin; and *Eli Lilly* relates to newly created human insulin protein.

In the instant case, applicants are not claiming a newly created nucleic acid or protein; rather, applicants are claiming a new general purpose primer for use in amplification experiments (claims 1-18 and 26-31) and a general purpose hybridization probe (claims 32-35). Through the inclusion of a blocking sequence, the dual-purpose of claims 1-18 and 26-31 facilitate the amplification of target sequences located within a secondary structure forming region by disrupting the secondary structures that otherwise prevent the target sequences from hybridizing to the dual-purpose primers. Similarly, through the inclusion of a blocking sequence, the

hybridization probe of claims 26-35 facilitates hybridization of the hybridization probe to a nucleotide sequence within a secondary structure forming region.

The foregoing discussion demonstrates that the cited case law does not support the position that the claimed dual-purpose and hybridization probes must be described with a sequence. Because the written description rejection is not based upon a proper legal or factual basis, applicants respectfully request that this Honorable Board find that the written description rejection is not proper and should be withdrawn.

C. CLAIMS 1-5, 9, 12-14, AND 26 ARE NOT ANTICIPATED BY WILTON ET AL.

Applicants appeal the rejection of claims 1-5, 9, 12-14, and 26 as anticipated under 35 U.S.C. § 102(b) by Wilton et al. For purposes of this appeal, claims 1-4 and 26 stand together; claims 5, 9, and 12 stand together; and claims 13 and 14 stand together.

1. CLAIMS 1-4 AND 26

As recited in claim 1, the present invention is directed to a dual-purpose primer for amplifying a target nucleotide sequence in a target molecule, wherein the target molecule has a secondary structure forming region and further wherein the target nucleotide sequence contains a site of interest proximal to or contained within the secondary structure forming region wherein the primer comprises: (a) a primer sequence complementary to a segment of the target nucleotide sequence other than the secondary structure forming region; and (b) a blocking sequence substantially complementary to a segment of the secondary structure forming region, wherein the blocking sequence disrupts formation of the unwanted secondary structure in an amplicon thereby enabling detection and amplification of the site of interest.

Claim 2, which is dependent on claim 1, recites that the site of interest is a nucleic acid sequence. Claim 3, which is dependent on claim 2, recites that the site of interest is a single nucleotide polymorphism. Claim 4, which is dependent on claim 1, recites that the primer sequence is complementary to one terminus of the target molecule containing the target nucleotide sequence. Claim 26, which is also dependent on claim 1, recites that the primer hybridizes to the target nucleic acid sequence via the action of a DNA polymerase.

With reference to claim 1, the claimed invention requires that the target nucleotide sequence (such as for example an SNP) is proximal to or contained within a secondary structure forming region of the target molecule. When the target molecule has such a configuration, the

dual-purpose primers are able to disrupt the secondary structure forming region of the target molecule so that the primer can detect and amplify the target nucleotide sequence.

Throughout the prosecution of the instant application, the Examiner has acknowledged that clause (a) of claim 1 recites a structural limitation. The basis of the Examiner's rejection of claim 1 lies in the Examiner's mistaken assertion that clause (b) recites a functional limitation of the claimed primers. While the recitation that the blocking sequence "disrupts formation of the unwanted secondary structure" is arguably a functional limitation, the recitation that the primer comprises "a blocking sequence substantially complementary to a segment of the secondary structure forming region" is unarguably a structural feature of the claimed primer.

The structural nature of the blocking sequence is disclosed throughout the specification. Directing the Board's attention to the figures of the instant application, Figure 5 depicts a schematic of the dual-purpose primer of the present invention. In Figure 5, the blocking sequence, shown by reference letter "B," is clearly shown as a structural segment of the primer. In paragraph 0019 (p.5, l.23, to p.6, l.3), the primer of Figure 5 is described as including a blocker sequence (B) and a primer sequence (P) wherein the P is complementary to one terminus of the target molecule that contains the SNP site (X) and B is substantially complementary to a sequence (B') immediately adjacent to X; B' being the segment of the target molecular responsible for generating an intramolecular secondary structure that in the absence of the dual-purpose primer would conceal the SNP site from a complementary sequence (thereby preventing hybridization and detection). After amplification of the target molecular sequence and reannealing, B hybridizes with B' thereby blocking formation of the unwanted secondary structure. *See also*, Paragraph 0057 (p.14, ll. 18-25). In Figure 7, the blocking sequence (shown in orange) is again clearly shown as a segment of the primer.

Figure 10 shows how the dual-purpose primer of the present invention anneals to two segments of a target nucleotide; specifically, one segment having the target SNP site located within an unwanted secondary structure region and another segment adjacent to the SNP site. As shown in Figure 10, the dual-purpose primer is able to anneal to two sections of the target nucleotide, which would otherwise not be accessible to amplification. By hybridizing to a segment within the secondary structure forming region, the blocking sequence of the dual-purpose primer of the present invention is able to disrupt the secondary structure forming region

thus allowing the ligation portion of the dual-purpose primer to hybridize to the SNP thereby making the amplification of the SNP site possible.

As shown in Figures 5, 7, and 10, the blocking sequence is a separate portion of the dual-purpose primer of the present invention, which may be adjacent to the priming sequence or separated from the priming sequence by a spacer. Without the blocking sequence, the primer of the present invention would not be able to carry out its dual-purpose, specifically, to block formation of secondary structure and to prime the SNP of interest.

Figures 4, 6, and 8 show the surprising and unexpected results that the dual-purpose primers of the present invention have on the detection of the SNP in exon 1 of the cytochrome P450 CYP2D6 gene. Figure 4 is a graph that shows how the blocking sequence enhances detection of exon 1 of the cytochrome P450 CYP2D2 gene (*see also*, para. 0018, p.5, ll. 20-22). In Figure 4, detection of exon 1 is measured at less than 10.0 with the conventional primer and in excess of 120.0 with the dual-purpose primer of the present invention. Figure 6 is a gel, which shows that the dual-purpose primers of the present invention with blocker sequence inserts of 8, 10, and 12 nucleotides all generate a major band of expected size (*see also*, para. 0020, p.6, ll. 4-5). In Figure 6, a 250 bp band for exon 1 is detected using the dual-purpose primer of the present invention with blocking sequences of 8, 10, and 12 nucleotides, but the band is barely detectable when the blocking sequence is not included in the primer (*see also*, para. 0095, p.25, ll. 9-10). The graph in Figure 8 shows how the blocking sequence of the claimed primer enhances the net signal in SNP assays over the signal obtained with a primer lacking the blocking sequence (para. 0022, p.6, ll. 4-5). In Figure 8, exon 1 is assayed for detection with the following three primers: (i) the dual-purpose primers of the present invention having blocking sequence of 8, 10, and 12 nucleotides; (ii) convention primers; and (iii) convention primers having an external blocker of 25 nucleotides (*see*, para. 0096, p.25, l.28 to p.26, l.6). As shown therein, the conventional primers do not show any appreciable detection of exon 1. While the conventional primers with the external blocker do show detection, the dual-purpose primers with the 10 and most notably with the 12 nucleotide blocking sequences show enhanced detection over the conventional primers with the 25 nucleotide external blocker.

The foregoing discussion of the present invention clearly shows that the blocking sequence is an integral structural feature of the claimed dual-purpose primers.

Turning to the cited reference, Wilton et al. teach snapback primers that are designed to produce a PCR product that forms and/or retains its secondary or tertiary structure so that the size of the PCR product may be determined by gel electrophoresis. The primers of Wilton et al. are shown in Figure 1. As stated in the Figure 1 legend, the snapback primers (Primer SB B(r) and Primer SB D(r)) are distinguished from the conventional primers by the additional 11 bases complementary to the sequence around the mdx mutation.

In Figure 1 of Wilton et al., the C to T mdx mutation was investigated using the following six primers: forward primer A (A(f)); reverse primer B (B(r)); forward primer (C(f)); reverse primer D (D(r)), reverse snapback primer B (SB-B(r)), and reverse snapback primer D (SB-D(r)). As explained on page 254 (col. 2, first full para.) of Wilton et al., the snapback primers SB-B(r) and SB-D(r) were designed from primers B(r) and D(r) with the addition at the 5' terminus of the primers of 11 bases complementary to the normal mouse dystrophin sequence around the location of the mdx mutation. PCR products generated from a forward primer (i.e., A(f) or C(f)) and either of the snapback primers have terminal sequences that when in single-stranded form reanneal or snapback to the area under investigation; in other words, the 3' terminus of the forward strand or the 5' terminus of the reverse strand have the potential to reanneal to the region of the mdx mutation, thus forming a secondary structure (*see*, p.256, col. 2).

Referencing Figure 3 of Wilton et al., the 3' terminus of the PCR product carrying the 11 bases complementary to the sequence around the mdx mutation (highlighted in bold) anneal or snapback back to the normal dystrophin sequence (highlighted with underlining) at the 5' terminus of the PCR product thereby causing the formation of a secondary structure with the mdx mutation being present *within* the secondary structure (*see* page 257, col. 2). As explained at pages 253 (col. 1), 257 (cols. 1 & 2), and 258 (col. 1) of Wilton et al., the conformation change resulting from the use of the snapback primers allows for the identification of the target nucleotides through altered migration of the target through a polyacrylamide gel.

The foregoing discussion highlights the differences between the dual-purpose primers of the present invention and the snapback primers of Wilton et al. Briefly, the snapback primers of Wilton et al. are designed to anneal to a *single* segment of a target nucleic acid such that PCR strands produced with the snapback primers have self-complementarity and are able to

“snapback” upon themselves to form a loop, i.e., a secondary or tertiary structure, with the target nucleic acid located *within* the loop. By contrast, the dual-purpose primer of the present invention is designed to anneal to *two* separate sections of a target nucleic acid - a segment outside of a secondary structure forming region and a segment within a secondary structure forming region - the end result being that the primer disrupts the secondary structure of the target nucleic acid to *expose* the target nucleic acid. Furthermore, unlike Wilton et al. where the reannealing of the oligonucleotide to form the secondary structure formation occurs *after* a priming cycle is complete, with the claimed invention, priming of the target nucleotide segment cannot *begin* until the secondary structure formation is disrupted.

The Examiner's rejection of the claims over Wilton et al. is the result of a search conducted only with search terms directed to clause (a) of claim 1. Proper consideration of the limitations of claim 1, specifically, the primer of clause (a) *and* the blocking sequence of clause (b), shows the impropriety of the Examiner's position.

2. CLAIMS 5, 9, AND 12

Claim 5, which is dependent on claim 1, recites that the dual-purpose primer further comprises a non-hybridizing spacer between the primer sequence and the blocking sequence. Claim 9, which is dependent on claim 5, recites that the non-hybridizing spacer is nucleotidic. Claim 12, which is dependent on claim 9, recites that the non-hybridizing spacer is an oligomeric segment of a recurring single nucleotide.

At page 6 of the Office Action (ll. 6-14), the Examiner improperly equates the 11 bases of the Wilton et al. primer (set forth in Figure 1, Table 1, and Figure 3 as Primer SB-B(r) and SB-D(r) with the 11 base sequence GCA ACA AAA TG) to the non-hybridizing spacer of the present invention (NFOA, p.6, ll. 6-9). Regarding claim 12, the Examiner improperly equates the recurring nucleotide A of the 11 base primer of Wilton et al. with the non-hybridizing oligomeric segment of claim 12 (NFOA, p.6, ll. 12-14).

Applicants submit that the 11 bases of the Wilton et al. primer are not comparable to the non-hybridizing spacer of the claimed dual-purpose primer. As is shown in Figure 3 of Wilton et al., the 11 bases are complementary to the sequence around the mdx mutation that are intended to reanneal back to the dystrophin sequence. By contrast, as shown in Figures 5 and 10 of the

instant application, the spacer sequence does not reanneal to the primer, rather, its function is strictly to separate the primer sequence from the blocking sequence.

Because the non-hybridizing sequence of claim 5 is not comparable to the 11 bases of Wilton et al., it follows that Wilton et al. do not anticipate the invention of claims 5-7.

3. CLAIMS 13 AND 14

Claim 13, which is dependent on claim 9, recites that the probe sequence and the spacer are separated from each other by a means for halting transcription therebetween. Claim 14, which is dependent on claim 13, recites that the means for halting transcription is an arresting linker.

At page 6 of the Office Action (ll. 15-23), the Examiner asserts that the means for language in claim 13 and the arresting linker of claim 14 are functional language (NFOA, p.6, ll. 20-23). Applicants disagree. It is well-established law that the means for claims are interpreted to include the structures disclosed in the specification. *See, e.g., Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 234 F.3d 558 (Fed. Cir. 2000) (en banc) (“A claim element recited in means-plus-function language literally encompasses the corresponding structure and its equivalents...In contrast, a claim element that recites the corresponding structure does not literally encompass equivalents of that structure.”). In this respect, applicants direct the Board's attention to paragraph 0043 (p.11, ll. 9-10) where the term “arresting linker” is expressly defined as “a nucleotidic or non-nucleotidic linker, in a probe or primer, which is not amplified by the amplification enzyme.” In paragraph 0059 of the specification (p.15, ll. 3-6), the means for halting transcription is defined generally as “a linker joining the two primer segments that prevents the polymerase used from continuing replication across the probe sequences – nucleotide spacer junction.” Lines 2-6 of paragraph 0059 (p.15) explain that the means for halting transcription includes arresting linkers and the remainder of paragraph 0059 provides examples of arresting linkers (p.15, ll. 7-17). In view of the foregoing, applicants submit that claims 13 and 14 do not recite functional language, but in fact recite structural limitations that must be considered by the Examiner.

D. CLAIMS 1, 2, AND 4-7 ARE NOT ANTICIPATED BY BANNWARTH ET AL.

Applicants appeal the rejection of claims 1, 2, and 4-7 as anticipated under 35 U.S.C. § 102(b) by Bannwarth et al. For purposes of this appeal, claims 1, 2, and 4 stand together and claims 5-7 stand alone.

1. CLAIMS 1, 2, AND 4

As recited in claim 1, the present invention is directed to a dual-purpose primer for amplifying a target nucleotide sequence in a target molecule, wherein the target molecule has a secondary structure forming region and further wherein the target nucleotide sequence contains a site of interest proximal to or contained within the secondary structure forming region wherein the primer comprises: (a) a primer sequence complementary to a segment of the target nucleotide sequence other than the secondary structure forming region; and (b) a blocking sequence substantially complementary to a segment of the secondary structure forming region, wherein the blocking sequence disrupts formation of the unwanted secondary structure in an amplicon thereby enabling detection and amplification of the site of interest.

Claim 2, which is dependent on claim 1, recites that the site of interest is a nucleic acid sequence. Claim 4, which is dependent on claim 1, recites that the primer sequence is complementary to one terminus of the target molecule containing the target nucleotide sequence.

With reference to claim 1, the claimed invention requires that the target nucleotide sequence in question is proximal to or contained within a secondary structure forming region of the target molecule. When the target molecule has such a configuration, the blocking sequence of the dual-purpose primer of the claimed invention is able to disrupt the secondary structure forming region of the target molecule so that the primer sequence can detect and amplify the target nucleotide sequence.

Bannwarth et al. teach a self-complementary oligonucleotide that backfolds upon itself in order to form a double-stranded section; the oligonucleotide formed in Bannwarth et al. is similar to the PCR product produced in Wilton et al. At col. 2, ll. 17-34, of Bannwarth et al., the structure of the oligonucleotide is described. The oligonucleotide of Bannwarth et al. consists of a sequence substantially complementary to a segment of a target nucleic acid (Pp); a non-nucleotidic linking sequence (L), which serves to facilitate the backfolding; a sequence substantially complementary to Pp (Pc); and an energy source (X), which is used for detecting

the oligonucleotide via energy transfer when the oligonucleotide is put in contact with a detection oligonucleotide. Figure 1 of Bannwarth et al. shows the configuration of the oligonucleotide when the Pp and Pc complementary strands anneal to form the double-stranded self-complementary oligonucleotide disclosed therein.

Bannwarth et al. do not teach or suggest that the oligonucleotide disclosed therein includes a sequence that is designed to block the formation of secondary structure formation.

As in the Wilton et al. rejection, the Examiner is taking the position that the language of clause (b) of claim 1 is functional language that has no patentable weight. By failing to give any patentable weight to the blocking sequence of clause (b), the Examiner is able to take the position that Bannwarth et al. anticipates the claims because it discloses an oligonucleotide with a sequence substantially complementary to a segment of a target nucleic acid (Pp).

The Examiner's rejection of the claims over Bannwarth et al. is the result of a search conducted only with search terms directed to clause (a) of claim 1. Proper consideration of the limitations of claim 1, specifically, the primer of clause (a) *and* the blocking sequence of clause (b), shows the impropriety of the Examiner's position.

2. CLAIMS 5-7

Claim 5, which is dependent on claim 1, recites that the dual-purpose primer further comprises a non-hybridizing spacer between the primer sequence and the blocking sequence. Claim 6, which is dependent on claim 5, recites that the spacer is non-nucleotidic. Claim 7, which is dependent on claim 6, recites that the spacer is comprised of a synthetic hydrophilic oligomer.

At page 8 of the Office Action (Il. 5-11), the Examiner incorrectly equates the linker of Bannwarth et al. with the non-hybridizing spacer of the claimed invention. Applicants submit that the linker of the Bannwarth et al. primer is not comparable to the non-hybridizing spacer of the claimed dual-purpose primer. As noted above, the linker of Bannwarth et al. is designed to facilitate the backfolding of the primer. By contrast, as recited in claim 5 and as shown in Figure 10 of the present invention, the non-hybridizing spacer of the claimed invention is designed to separate the primer sequence from the blocking sequence.

Because the non-hybridizing sequence of claim 5 is not comparable to the Bannwarth et al. linker, it follows that Bannwarth et al. do not anticipate the invention of claims 5-7.

E. CLAIMS 1 AND 5-8 ARE NOT ANTICIPATED BY LAIBINIS ET AL.

Applicants appeal the rejection of claims 1 and 5-8 as anticipated under 35 U.S.C. § 102(b) by Laibinis et al. For purposes of this appeal claim 1 stands alone and claims 5-8 stand together.

1. CLAIM 1

As recited in claim 1, the present invention is directed to a dual-purpose primer for amplifying a target nucleotide sequence in a target molecule, wherein the target molecule has a secondary structure forming region and further wherein the target nucleotide sequence contains a site of interest proximal to or contained within the secondary structure forming region wherein the primer comprises: (a) a primer sequence complementary to a segment of the target nucleotide sequence other than the secondary structure forming region; and (b) a blocking sequence substantially complementary to a segment of the secondary structure forming region, wherein the blocking sequence disrupts formation of the unwanted secondary structure in an amplicon thereby enabling detection and amplification of the site of interest.

With reference to claim 1, the claimed invention requires that the target nucleotide sequence in question is proximal to or contained within a secondary structure forming region of the target molecule. When the target molecule has such a configuration, the blocking sequence of the dual-purpose primer of the claimed invention is able to disrupt the secondary structure forming region of the target molecule so that the primer sequence can detect and amplify the target nucleotide sequence.

Laibinis et al. teach a method for covalently linking a nucleic acid molecule having a target moiety to a support-bound oligonucleotide (i.e., a capture probe). The nucleic acid molecule is hybridized to the capture probe via a complementary sequence, i.e., a pairing sequence on the nucleic acid molecule, which is covalently bound to a complementary sequence on the capture probe (para. 0010). Paragraph 0010 (p.1, col. 2 to p.2, col. 1) and Figure 4 describe the oligonucleotide of Laibinis et al. The only mention in Laibinis et al. with respect to secondary or tertiary structure is at paragraph 0132 (p.12, col. 2) where it is stated that the target moiety may include secondary or tertiary structure. Laibinis et al. do not teach or suggest that the structures may be problematic and does not teach, suggest, or contemplate any reason or way to disrupt the secondary structure formation.

As with the Wilton et al. and Bannwarth et al. rejections, the Examiner is taking the position that the language of clause (b) of claim 1 is functional language that has no patentable weight. By failing to give any patentable weight to the blocking sequence of clause (b), the Examiner is able to take the position that Laibinis et al. anticipates the claims because it discloses a capture probe with a sequence substantially complementary to a segment of a target nucleic acid.

The Examiner's rejection of the claims over Laibinis et al. is the result of a search conducted only with search terms directed to clause (a) of claim 1. Proper consideration of the limitations of claim 1, specifically, the primer of clause (a) *and* the blocking sequence of clause (b), shows the impropriety of the Examiner's position.

2. CLAIMS 5-8

Claim 5, which is dependent on claim 1, recites that the dual-purpose primer further comprises a non-hybridizing spacer between the primer sequence and the blocking sequence. Claim 6, which is dependent on claim 5, recites that the spacer is non-nucleotidic. Claim 7, which is dependent on claim 6, recites that the spacer is comprised of a synthetic hydrophilic oligomer. Claim 8, which is dependent on claim 7, recites that spacer is comprised of about 3 to about 50 alkylene oxide units selected from ethylene oxide and combinations of ethylene oxide and propylene oxide.

At page 9 of the Office Action (ll. 10-13), the Examiner incorrectly equates the linking moiety of Laibinis et al. with the non-hybridizing spacer of the present invention. At paragraph 0014 (p.2, col. 1) of Laibinis et al., it is disclosed that a linking moiety, which may be an alkylene chain, may be used to link the nucleic acid probe to the pairing sequence. As explained in paragraph 0037 (p.3, col. 1), the target moiety of Laibinis et al. is attached to the nucleic acid probe, which is attached either directly or through a linking moiety to a pairing sequence, which has a complement on a substrate bound capture probe.

Applicants submit that the linking moiety of the Laibinis et al. is not comparable to the non-hybridizing spacer of the claimed invention. The non-hybridizing spacer of the present invention separates the blocking sequence and the primer sequence. Figures 5 and 10 show a schematic representation of a non-hybridizing spacer of the present invention. As shown therein, the non-hybridizing spacer participates in the secondary structure disruption of the claimed

dual-purpose primers so that the target nucleotide may be detected and amplified. By contrast, in Laibinis, the linking moiety serves to separate the nucleic acid carrying the target moiety from the pairing sequence that binds to the capture probe.

Because the non-hybridizing spacer of claim 5 is not comparable to the Laibinis et al. linking moiety, it follows that Laibinis et al. do not anticipate the invention of claims 5-8.

F. CLAIMS 1, 17, AND 18 ARE NOT ANTICIPATED BY BEATTIE ET AL.

Applicants appeal the rejection of claims 1, 17, and 18 as anticipated under 35 U.S.C. § 102(b) by Beattie et al. For purposes of this appeal, claims 1, 17, and 18 stand together.

As recited in claim 1, the present invention is directed to a dual-purpose primer for amplifying a target nucleotide sequence in a target molecule, wherein the target molecule has a secondary structure forming region and further wherein the target nucleotide sequence contains a site of interest proximal to or contained within the secondary structure forming region wherein the primer comprises: (a) a primer sequence complementary to a segment of the target nucleotide sequence other than the secondary structure forming region; and (b) a blocking sequence substantially complementary to a segment of the secondary structure forming region, wherein the blocking sequence disrupts formation of the unwanted secondary structure in an amplicon thereby enabling detection and amplification of the site of interest.

Claim 17, which is dependent on claim 1, recites that the dual-purpose primer further comprises a detectable label. Claim 18, which is dependent on claim 17, recites that the detectable label is selected from the group consisting of fluorescers, chemilumescers, dyes, biotin, haptens, enzymes, enzyme substrates, enzyme cofactors, enzyme inhibitors, enzyme subunits, metal ions, electron-dense reagents, and radioactive isotopes.

With reference to claim 1, the claimed invention requires that the target nucleotide sequence in question is proximal to or contained within a secondary structure forming region of the target molecule. When the target molecule has such a configuration, the blocking sequence of the dual-purpose primer of the claimed invention is able to disrupt the secondary structure forming region of the target molecule so that the primer sequence can detect and amplify the target nucleotide sequence.

Beattie et al. teach the tandem hybridization of labeled oligonucleotides to a heat-denatured strand of double-stranded DNA in order to avoid the spontaneous formation of

secondary structures in the single-stranded target nucleotide. The difference between the dual-purpose primer of the present invention and the tandem hybridization technique described in Beattie et al. is most evident when Figures 5 and 10 of the instant application are compared against 13A, 13B, 14A, 14B, 15A, and 15B of Beattie et al.

Figures 5 and 10 of the instant application are explained above under the discussion of Wilton et al.

As shown in Figures 13A and 13B, the hybridization technique of Beattie et al. includes hybridization of a molar excess of labeled oligonucleotides in tandem to a heat-denatured target strand of a double-stranded target DNA (*see also*, col. 7, l.66, to col. 8, l.8). As is shown in Figures 14A and 14B, the probes of Beattie et al. do *not* have blocking sequences. Further, as is clear from Figures 13 to 15, as well as the text of Beattie et al. (*see, e.g.*, col. 7, ll. 7-63), the Beattie et al. probes are intended only to identify the sequence of a target analyte and not to amplify the target strand.

The Examiner's rejection of the claims over Beattie et al. is the result of a search conducted only with search terms directed to clause (a) of claim 1. Proper consideration of the limitations of claim 1, specifically, the primer of clause (a) *and* the blocking sequence of clause (b), shows the impropriety of the Examiner's position.

G. CLAIMS 27-32 ARE NOT OBVIOUS OVER WILTON ET AL.

IN VIEW OF STRATAGENE

Applicants appeal the rejection of claims 27-32 as obvious under 35 U.S.C. § 103(a) over Wilton et al. in view of Stratagene. For purposes of this appeal, claims 27-31 stand together and claim 32 stands with claim 1.

The differences between the claimed invention and the primary reference, Wilton et al., are discussed above in the traversal to the anticipation rejection of claims 1-5, 9, 12-14, and 26 by Wilton et al.

1. CLAIMS 27-31

Claims 27-31, which depend from claim 1, are directed to a kit for determining the genotype of an individual.

At page 12 of the Office Action (l.13), the Examiner acknowledges that Wilton et al. do not teach a kit and cites Stratagene for the missing teaching.

Because Wilton et al. do not teach or suggest the dual-purpose primer of claim 1 for the reasons discussed above in the traversal to the Wilton et al. anticipation rejection, it follows that the additional teaching from the Stratagene catalog will not serve to render claims 27-31 obvious.

2. CLAIM 32

Claim 32, which is an independent claim, is directed to a hybridization probe comprising (a) a probe nucleotide sequence complementary to a first nucleotide sequence in a target molecule, and (b) a blocking sequence substantially complementary to a second nucleotide sequence located within a secondary structure formation in the target molecule, wherein the secondary structure formation interferes with hybridization of the probe nucleotide sequence to the first nucleotide sequence and further wherein hybridization of the blocking sequence with the second nucleotide sequence disrupts the secondary structure formation in the second nucleotide sequence such that the probe nucleotide sequence is able to hybridize to the first nucleotide sequence.

The rejection of claim 32 is set forth in the Office Action at page 12, lines 1-12. The rejection does not explain how the teachings from the secondary reference render claim 32 obvious. Because claim 32 is not directed to a kit, the teachings from the Stratagene catalog do not appear to apply to this claim. For the foregoing reason, the discussion in traverse of the anticipation rejection of claim 1 over Wilton et al. applies with equal force to claim 32.

H. CLAIM 28 IS NOT OBVIOUS OVER BANNWARTH ET AL. IN VIEW OF STRATAGENE

Applicants appeal the rejection of claim 28 as obvious over Bannwarth et al. in view of the Stratagene Catalog. For purposes of this appeal, claim 28 stands alone.

The differences between the claimed invention and the primary reference, Bannwarth et al., are discussed above in the traversal to the anticipation rejection of claims 1, 2, and 4-7 by Bannwarth et al.

Claim 28, which is dependent on claim 1, is directed to a kit for determining the genotype of an individual.

At page 13 of the Office Action (I.16), the Examiner acknowledges that Bannwarth et al. do not teach a kit and cites Stratagene for the missing teaching.

Because Bannwarth et al. do not teach or suggest the dual-purpose primer of claim 1 for the reasons discussed above in the traversal to Bannwarth et al. anticipation rejection, it follows that the additional teaching from the Stratagene catalog will not serve to render claim 28 obvious.

I. CLAIMS 28-34 ARE NOT OBVIOUS OVER BEATTIE ET AL.

IN VIEW OF STRATAGENE

Applicants appeal the rejection of claims 28-34 as obvious over Beattie et al. in view of the Stratagene Catalog. For purposes of this appeal, claims 28-31 stand together and claims 32-34 stand with claim 1.

The differences between the claimed invention and the primary reference, Beattie et al., are discussed above in the traversal to the anticipation rejection of claims 1, 17, and 18 by Beattie et al.

1. CLAIMS 28-31

Claims 28-31, which are dependent on claim 1, are directed to a kit for determining the genotype of an individual.

At page 15 of the Office Action (l.21), the Examiner acknowledges that Beattie et al. do not teach a kit and cites Stratagene for the missing teaching.

Because Beattie et al. do not teach or suggest the dual-purpose primer of claim 1 for the reasons discussed above in the traversal to Beattie et al. anticipation rejection, it follows that the additional teaching from the Stratagene catalog will not serve to render claims 28-31 obvious.

2. CLAIM 32-34

Claims 32-34 are directed to a hybridization probe. The rejection of claim 32 is set forth in the Office Action at page 15, lines 6-20. The rejection does not explain how the teachings from the secondary reference render claims 32-34 obvious.

Because claims 32-34 are not directed to a kit, the teachings from the Stratagene catalog do not appear to apply to this claim. For the foregoing reason, the discussion in traverse of the anticipation rejection of claim 1 over Wilton et al. applies with equal force to claims 32-34.

J. CLAIMS 10, 11, 15, AND 16 ARE NOT OBVIOUS OVER WILTON ET AL.

IN VIEW OF FISHER

Applicants appeal the rejection of claims 10, 11, 15, and 16 as obvious over Wilton et al. in view of Fisher et al. For purposes of this appeal, claims 10, 11, 15, and 16 stand together.

The differences between the claimed invention and the primary reference, Wilton et al., are discussed above in the traversal to the anticipation rejection of claims 1-5, 9, 12-14, and 26 by Wilton et al.

Claims 10, 11, 15, and 16 all ultimately depend from claim 1. Claim 10 recites that the non-hybridizing spacer of claims 5 and 9 is comprised of a sequence of non-natural nucleotides. Claim 11 recites that the non-natural nucleotides of claim 10 are selected from iso-guanine and iso-cytosine. Claim 15 recites that the arresting linker of claim 14 comprises at least one modified nucleoside. Claim 16 recites that the modified nucleoside of claim 15 is a N⁴-modified pyrimidine.

The Examiner cites the secondary reference, Fisher et al., for the non-natural nucleosides of claims 10 and 11 and the modified nucleosides of claims 15 and 16.

Because Wilton et al. do not teach or suggest the dual-purpose primer of claim 1 for the reasons discussed above in the traversal to the Wilton et al. anticipation rejection, it follows that the additional teaching from Fisher et al. will not serve to render claims 27-31 obvious.

K. THE CLAIM TERM "SUBSTANTIALLY COMPLEMENTARY" IS PROPER

At page 17 of the Office Action (p.17, No. 12), the Examiner provides rebuttal arguments to applicants' arguments in the response filed on October 17, 2007. Although not the subject of a rejection, the Examiner's rebuttal arguments, which have the flavor of an indefiniteness rejection, are part of the record and address subject matter that is of consequence in the rejections. For the foregoing reasons, applicants respectfully request the Board's consideration of the Examiner's rebuttal arguments.

As background, the subject matter of the rebuttal arguments stem back to the Office Action of Aug. 7, 2007 (pp. 14-16); there, in the sentence bridging pp. 14-15, the Examiner acknowledges that the phrase "substantially complementary to another nucleotide sequence" from the blocking sequence recitation of the claims is a structural limitation. Nevertheless, the Examiner argues that because the term "substantially" is not defined, a single nucleotide match reads on the claims. In the response filed on Oct. 7, 2007, applicants directed the Examiner's attention to paragraph 0042 of the specification, which defines "substantially complementary" as meaning "at least about 80% complementarity." In the Office Action under reply, the Examiner argues that the term "substantially complementary" is not defined because one of ordinary skill in

the art would not understand the meaning of the term “at least about 80%.” The Examiner’s position is that the ordinary artisan would not understand the term because he or she would interpret the word “about” to include numbers on either side of 80 and the term “at least” to only include numbers less than 80 leading to indefinite confusion. Applicants position is that the word “about” is generally known to mean “approaching some degree of exactness” and that the ordinary artisan would readily understand that the word “about” in the term “at least about 80%” would only refer to those values that are slightly above 80%.

Near the middle of page 17 of the Office Action, the Examiner cites *Amgen v. Chugai*, 927 F.2d 1200 (Fed. Cir. 1991) for legal support. Applicants submit that this case does not support the position taken. The *Amgen* Court did not find that the claim term “at least about 160,000” (in reference to specific activity of EPO) to be indefinite because of the language of the term; rather, the claim was held invalid because the Court found that the addition of the word “about” to the claim was an attempt to recapture mean specific activity that was anticipated by the prior art. *Amgen*, 927 F.2d at 1217-1218.

While the Examiner’s position is not the subject of a rejection, because this issue concerns important claim language, applicants respectfully request that this Honorable Board adopt applicants' interpretation of the claim term “substantially complementary” and acknowledge that the claim term is clear, defined, and readily understood by one of ordinary skill in the art.

VIII. CONCLUSION

The foregoing discussion identifies the clear errors in fact and law in the rejections of the claimed invention. Because the claimed invention is supported by the written description as filed and is not anticipated by or rendered obvious by the cited references, applicants respectfully request that this Honorable Board withdraw the rejections from the outstanding Office Action and allow the subject application to pass to issue.

Respectfully submitted,

By: /Karen Canaan/
Karen Canaan, Esq.
Registration No. 42,382
Sheppard, Mullin, Richter & Hampton, LLP
2225 E. Bayshore Rd., Suite 205
Palo Alto, California 94303

IX. CLAIMS APPENDIX

1. **(Previously presented)** A dual-purpose primer for amplifying a target nucleotide sequence in a target molecule, wherein the target molecule has a secondary structure forming region and further wherein the target nucleotide sequence contains a site of interest proximal to or contained within the secondary structure forming region wherein the primer comprises: (a) a primer sequence complementary to a segment of the target nucleotide sequence other than the secondary structure forming region; and (b) a blocking sequence substantially complementary to a segment of the secondary structure forming region, wherein the blocking sequence disrupts formation of the unwanted secondary structure in an amplicon thereby enabling detection and amplification of the site of interest.

2. **(Original)** The primer of claim 1, wherein the site of interest is a nucleic acid sequence.

3. **(Original)** The primer of claim 2, wherein the site of interest is a single nucleotide polymorphism.

4. **(Original)** The primer of claim 1, wherein the primer sequence is complementary to one terminus of the target molecule containing the target nucleotide sequence.

5. **(Original)** The primer of claim 1, further including a nonhybridizing spacer between the primer sequence and the blocking sequence.

6. **(Original)** The primer of claim 5, wherein the spacer is non-nucleotidic.

7. **(Original)** The primer of claim 6, wherein the spacer is comprised of a synthetic hydrophilic oligomer.

8. **(Original)** The primer of claim 7, wherein the spacer is comprised of about 3 to about 50 alkylene oxide units selected from ethylene oxide and combinations of ethylene oxide and propylene oxide.

9. **(Original)** The primer of claim 5, wherein the spacer is nucleotidic.

10. **(Original)** The primer of claim 9, wherein the spacer is comprised of a sequence of non-natural nucleotides.

11. **(Original)** The primer of claim 10, wherein the non-natural nucleotides are selected from iso-guanine and iso-cytosine.

12. **(Previously presented)** The primer of claim 9, wherein the spacer is an oligomeric segment of a recurring single nucleotide.

13. **(Original)** The primer of claim 9, wherein the probe sequence and the spacer are separated from each other by a means for halting transcription therebetween.

14. **(Original)** The primer of claim 13, wherein the means for halting transcription is an arresting linker.

15. **(Original)** The primer of claim 14, wherein the arresting linker comprises at least one modified nucleoside.

16. **(Original)** The primer of claim 15, wherein the modified nucleoside is an N⁴-modified pyrimidine.

17. **(Original)** The primer of claim 1, further comprising a detectable label.

18. **(Original)** The primer of claim 17, wherein the detectable label is selected from the group consisting of fluorescers, chemiluminescers, dyes, biotin, haptens, enzymes, enzyme substrates, enzyme cofactors, enzyme inhibitors, enzyme subunits, metal ions, electron-dense reagents, and radioactive isotopes.

26. **(Original)** An amplicon formed by the action of a DNA polymerase on the primer of claim 1 hybridized to the target nucleotide sequence.

27. **(Original)** A kit for determining the genotype of an individual, comprising a dual-purpose primer according to claim 1, nucleotides appropriate to amplification of an oligonucleotide sequence, and an agent for polymerization of the nucleotides.

28. **(Original)** A kit for determining the genotype of an individual, comprising a dual-purpose primer according to claim 1, a second primer, nucleotides appropriate to DNA amplification, an agent for polymerization of the nucleotides, an allele specific hybridization (ASH) probe having a nucleotide capture region, and color-coded detecting means having a nucleotide capture region complementary to the nucleotide capture region on said ASH probe, wherein the nucleotide capture region on said detecting means is complementary to said ASH probe such that the target nucleotide sequence is identified by the color-coding of said detecting means.

29. **(Original)** The kit of claim 28, wherein the detecting means is a multiplex detecting means.

30. **(Original)** The kit of claim 29, wherein the multiplex detecting means comprises a detectable solid substrate.

31. **(Original)** The kit of claim 30, wherein the detectable solid substrate is a detectable microsphere.

32. **(Previously presented)** A hybridization probe comprising (a) a probe nucleotide sequence complementary to a first nucleotide sequence in a target molecule, and (b) a blocking sequence substantially complementary to a second nucleotide sequence located within a secondary structure formation in the target molecule, wherein the secondary structure formation interferes with hybridization of the probe nucleotide sequence to the first nucleotide sequence and further wherein hybridization of the blocking sequence with the second nucleotide sequence disrupts the secondary structure formation in the second nucleotide sequence such that the probe nucleotide sequence is able to hybridize to the first nucleotide sequence.

33. **(Original)** The hybridization probe of claim 32, further comprising a detectable label.

34. **(Original)** The hybridization probe of claim 33, wherein the detectable label is selected from the group consisting of chemiluminescent labels, fluorescent labels, radioactive labels, multimeric DNA labels, dyes, enzymes, enzyme modulators, detectable solid substrates, and metal ions.

35. **(Previously presented)** A method of performing a hybridization assay for detecting the presence of a target nucleotide sequence in a target molecule, wherein the target nucleotide sequence is proximal to or contained within a secondary structure forming region capable of forming an unwanted secondary structure that would prevent detection of the target nucleotide sequence, the method comprising: contacting the target molecule under hybridizing conditions with the hybridization probe of claim 33, such that hybridization of the probe to the target molecule disrupts formation of the unwanted secondary structure and allows detection of the target nucleotide sequence.

X. EVIDENCE APPENDIX

None.

XI. RELATED PROCEEDINGS APPENDIX

None.